REMARKS

I. Status of the Claims

Claims 4, 6-8, 17, 20-28, and 48 are pending in the application following entry of this amendment. Claim 6 has been amended. Claim 47 has been canceled without prejudice to pursuing the claim in a continuing application. Support for amendment to the claims can be found throughout the specification, and for example, on page 10, line 18 to page 11, line 2.

Claims 4, 6-8, 17, 20-28 are rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. Claims 4, 6-8, 17, 20-28, 47 and 48 are rejected under 35 U.S.C. § 112, first paragraph as failing to comply with the enablement requirement. The examiner stated that the claims are free of the prior art of record.

II. The claims are patentable under 35 U.S.C. § 112, paragraph 1

A. Written Description

Claims 4, 6-8, 17, and 20-28 were rejected under 35 U.S.C. § 112, first paragraph, for allegedly lacking written description for use of the term "5'-UTR" to refer to any 5'-UTR from any gene.

Without acceding to the examiner's rejection, claim 6 has been amended to include the limitation of claim 47 and claim 47 has been cancelled in the current amendment without prejudice to pursuing the claims in a continuing application. The rejection of claims 4, 6-8, 17, and 20-28 for lacking written description is moot. Accordingly, applicants respectfully request that the rejection of claims 4, 6-8, 17, and 20-28 under 35 U.S.C. § 112, first paragraph, be withdrawn.

B. Enablement

Claims 4, 6-8, 17, 20-28, 47 and 48 were rejected under 35 U.S.C. § 112, first paragraph, for allegedly containing non-enabled subject matter. The examiner alleges that the specification, while being enabling for a recombinant nucleic acid molecule consisting of a nucleotide sequence encoding hepatitis C virus nonstructural proteins NS3, NS4 and NS5, wherein said nucleotide sequence is operably linked to regulatory elements, said regulatory elements comprising a promoter, enhancer, polyadenylation sequence, and at most the 9 most

3' nucleotides of the 5'UTR of a hepatitis C virus, does not reasonably provide enablement for a recombinant nucleic acid molecule consisting of a nucleotide sequence encoding hepatitis C virus nonstructural proteins NS3, NS4 and NS5, wherein said nucleotide sequence is operably linked to regulatory elements, said regulatory elements comprising a promoter, enhancer, polyadenylation sequence, and a 5' untranslated region from any gene. Applicants traverse the rejection.

Applicants' claimed invention, as amended, is a recombinant nucleic acid molecule consisting of a nucleotide sequence encoding hepatitis C virus nonstructural proteins NS3, NS4 and NS5, wherein said nucleotide sequence is operably linked to regulatory elements, said regulatory elements comprising a promoter, enhancer, polyadenylation sequence, and a hepatitis C virus 5'UTR. Furthermore, the claimed invention is a method of inducing an immune response against hepatitis C virus in a human uninfected by hepatitis C virus comprising administering the recombinant nucleic acid molecule. The specification is enabling for the claimed invention. The specification states that the 5'-UTR can include the last 9 nucleotides of the HCV 5'-UTR, the last 50 nucleotides, the last 100 nucleotides, the last 150 nucleotides, the last 200 nucleotides the last 250 nucleotides, the last 300 nucleotides, or the entire HCV 5' UTR. See specification, for example, page 10, line 18 to page 11, line 2. All of these proportionate lengths of HCV 5' UTR are functional in an expression construct comprising a nucleic acid encoding the HCV NS3, NS4, and NS5 genes. The specification, as filed, and subsequent publications that are currently of record support the transcriptional activity of expression constructs incorporating the HCV 5' UTR.

The Examiner points to a statement by Selby et al., and states that "the full length 5' UTR inhibits expression of viral genes (see first full paragraph on page 1105 right column in Selby et al *J. Gen. Virol.* **74:** 1103-1113, 1993, of record). Selby et al further observed that 5' leader does not promote efficient translation. This statement in Selby does not lead one to the conclusion stated by the Examiner that "it is not clear whether the claimed construct would produce sufficient protein to produce an immune response." See Office Action, Paper No. 11, page 7. The absolute quantity of protein produced by a DNA expression vector does not necessarily correlate with the level of immune response in a mammalian subject. In particular, the results of Tokushige et al., *Hepatology*, **24**:14-20, 1996 (of record) indicate

that the intact HCV 5' UTR provides sufficient intracellular expression of HCV core protein to produce immune reactive HCV core protein on a Western blot. See Tokushige et al., Figure 1B. Because protein expression from a construct comprising the HCV 5' UTR would produce lower levels of gene expression, it does not necessarily follow, as urged by the Examiner, that "it is not clear whether the claimed construct would produce sufficient protein to produce an immune response."

Yoo et al., *Virology* **191:** 889-899, 1992 (of record) measured transient expression from an expression construct with a chloramphenicol transferase (CAT) reporter and a promoter region including various regions of the HCV 5' UTR. These experiments mapped the *cis*-acting elements controlling translation in the HCV genome linking a full length (nucleotides 1 to 341) or deleted versions of the 5' UTR of HCV RNA to the coding region of CAT mRNA. See, for example, Figure 1 of Yoo et al. As stated in the Declaration by Dr. Jack Wands in Paper No. 13:

> "Utilizing information provided in the subject application and in Yoo et al. *Virology* **191**: 889-899, 1992, one skilled in the art would understand the function of the 5' UTR of hepatitis C virus, including the positive and negative translational control elements within the 5'-UTR. One skilled in the art would be able to operably link the 5'UTR of hepatitis C virus to a recombinant nucleic acid molecule acting as an expression plasmid for proteins, for example, hepatitis C virus non-structural (NS) protein."
>
> Declaration of Dr. Jack Wands under 37 C.F.R. § 1.132 in Paper No. 13.

Therefore a person of skill in the art would know how to utilize the HCV 5' UTR to enhance expression of the HCV NS3, NS4, and NS5 proteins. The specification enables one of skill in the art to utilize various regions of the 5' UTR of a hepatitis C virus (*i.e.*, more than "at most the 9 most 3' nucleotides of the 5' UTR of a hepatitis C virus") to construct a recombinant nucleic acid molecule as claimed. Furthermore, as stated above, Tokushigi et al. show that the intact HCV 5' UTR provides sufficient intracellular expression of HCV core protein to produce immune reactive HCV core protein on a Western blot. Therefore, the specification enables one of skill in the art to utilize various regions of the 5' UTR of a hepatitis C virus to construct and use a recombinant nucleic acid molecule encoding HCV NS3, NS4, and NS5 in a method of inducing an immune response against hepatitis C virus in a human uninfected by hepatitis C virus.

With respect to the teachings of a specification disclosure, the following statement from *In re Manocchi,* 169 U.S.P.Q. 367, 369-370 (C.C.P.A. 1971), is noteworthy:

> The only relevant concern of the Patent Office under these circumstances should be over the truth of any such assertion. The first paragraph of § 112 requires nothing more than objective enablement. How such a teaching is set forth, either by the use of illustrative examples or by broad terminology, is of no importance.
>
> As a matter of Patent Office practice, then, a specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as in compliance with the enabling requirements of the first paragraph of § 112 unless there is reason to doubt the objective truth of the statements contained therein which must be relied upon for enabling support.
> *In re Manocchi,* 169 U.S.P.Q. 367, 369-370 (C.C.P.A. 1971).

The examiner has no reason to doubt the objective truth of the statements contained in the application teaching the manner and process of making the claimed invention. Applicants' claimed invention is fully enabled as a nucleic acid molecule, a pharmaceutical composition and a method of inducing an immune response with a recombinant nucleic acid molecule comprising genes for NS proteins and the 5'-UTR of hepatitis C virus. The specification discloses and one skilled in the art would know, for example, as evidenced by Dr. Wands' declaration, and by Tokushige et al. and Encke et al., that the NS proteins expressed by the claimed nucleic acid molecule including the HCV 5' UTR would function at a sufficient level of expression and would produce a sufficient humoral and CTL immune response in a human. The examiner has not provided evidence sufficient to doubt the truth of the disclosure stating that the claimed compositions and methods produce a sufficient immune response in a human.

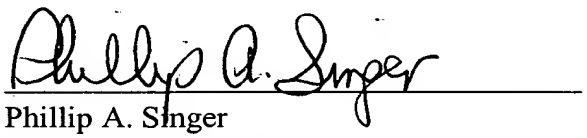
Accordingly, applicants respectfully request that the rejection of claims 4, 6-8, 17, and 20-28 and 48 under 35 U.S.C. § 112, first paragraph, be withdrawn.

III. Conclusion

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 206-332-1380.

Date: April 25, 2005



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